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AWARD NUMBER: W81XWH-14-1-0025

TITLE: Effect of Prazosin and Naltrexone on Script Induced Alcohol Craving in Veterans with Alcohol Use Disorders with and without Co-occurring PTSD

PRINCIPAL INVESTIGATOR: Tracy Simpson, PhD

RECIPIENT: Seattle Institute for Biomedical and Clinical Research
Seattle, WA 98108

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Fort Detrick, Maryland 21702-5012

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Effect of Prazosin and Naltrexone on Script Induced Alcohol Craving in Veterans with Alcohol Use Disorders with and without Co-occurring PTSD

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6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Background: Military personnel are at risk for developing hazardous drinking patterns post-deployment that can negatively impact their health and psychiatric stability. This phenomenon is compounded by the fact that despite recent gains in establishing effective pharmacological and behavioral treatments for alcohol use disorders (AUD), nonremittance and relapse remain major problems for those with AUDs. One individual factor that is strongly associated with continued problematic use and relapse is craving. Three different types of craving have been hypothesized, reward, relief, and obsessive, and each is postulated to be mediated by different neurological substrates. The neural networks postulated to subserve reward and relief craving receive afferents from and project to noradrenergic neurons in non-human primates and humans express α1 adrenergic receptors. Given the interplay of the noradrenergic system with craving-related brain systems, blocking α1 receptors with the noradrenergic antagonist, prazosin, theoretically has the potential to modulate reward and relief craving.

Objective/Hypotheses: The overarching objective of the study is to evaluate whether prazosin alone and/or in conjunction with naltrexone is effective at reducing reward and relief craving for alcohol among veterans with an AUD in both a human laboratory context and in their day-to-day lives via daily symptom telephone monitoring using Interactive Voice Response (IVR). The proposed study also seeks to evaluate whether specific individual characteristics, including PTSD status, moderate medication response.

15. SUBJECT TERMS

Alcohol Drinking, Drinking Behavior, Naltrexone, Prazosin, Adrenergic Agents, Adrenergice Antagonists, Adrenergic alpha-1 receptor antagonists, Adrenergic alpha-antagonists, Antihypertensive agents, Narcotic antagonists, Therapeutic uses

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	10	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

   Recently deployed Veterans are at risk of developing hazardous drinking patterns post-deployment. Craving is strongly associated with continued problematic use and relapse. The noradrenergic system subserves craving-related brain systems. Blocking α1 receptors with the noradrenergic antagonist, prazosin has the potential to modulate craving. 120 Veterans with an alcohol use disorder (AUD) will be randomized to receive prazosin, naltrexone, both medications, or placebo for 3 weeks. The purpose of this study is to see whether the drugs prazosin and naltrexone will decrease alcohol cravings and drinking in individuals who have problems with alcohol and have used alcohol at risky levels in the past 90 days.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

   Alcohol Drinking
   Drinking Behavior
   Alcohol Craving
   Naltrexone
   Prazosin
   Adrenergic Agents
   Adrenergic Antagonists
   Adrenergic alpha-1 Receptor Antagonists
   Adrenergic alpha-Antagonists
   Antihypertensive Agents
   Cardiovascular Agents
   Central Nervous System Agents
   Molecular Mechanisms of Pharmacological Action
   Narcotic Antagonists
   Neurotransmitter Agents
   Peripheral Nervous System Agents
   Pharmacologic Actions
   Physiological Effects of Drugs
   Sensory System Agents
   Therapeutic Uses

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

   What were the major goals of the project?
   See beneath for the study's scope of work table which lists major project goals.

What was accomplished under these goals?

Specific Aim 1: To compare the effects of prazosin only, naltrexone only, and their combination to placebo control on reward oriented and relief oriented alcohol craving elicited by personalized imaginal scripts in a human laboratory setting.				
Specific Aim 2: To determine the effect of the four medication conditions on day-to-day reports of alcohol craving and drinking motives via daily telephone IVR.				
Specific Aim 3: Explore whether PTSD status moderates medication response.				
Year:	1	2	3	4
Preparatory Tasks				
Task 1: Obtain all necessary regulatory approvals (IRB, R&D, biohazard)	X			
Task 2: Hire research staff (recruit study RA; study clinician is already in lab)	X			
Task 3: Purchase medication; have study medications compounded	X			
Task 4: Set up pharmacy dispensing, including randomization protocol	X			
Task 5: Set up agreement with VA laboratory for blood and urine assays	X			
Task 6: Finalize case report forms	X			
Task 7: Train clinician on Clinician Administered PTSD Scale; establish reliability	X			
Task 8: Work with Data Systems Inc. to program IVR system	X			
Task 9: Set up recruitment systems	X			
Task 10: Set up participant payment and purchase order systems w/ SIBCR	X			
Preparatory Milestones: Tasks 1 - 10 will be completed by the end of month 6				
Recruitment and Retention Tasks				
Task 11: Initiate recruitment and retention efforts	X	X	X	
Task 12: Recruit and retain Veterans and National Guard/Reserve Members with an AUD and recent alcohol craving.	X	X	X	
Recruitment and Retention Milestones:				
• By the end of Year 1 20 Veterans and/or NG/R members will have been recruited				
• By the end of Year 2 60 Veterans and/or NG/R members will have been recruited				
• By the end of Year 3 100 Veterans and/or NG/R members will have been recruited				
• At the end of the first 6 months of Year 4 the total sample of 120 Veterans and/or NG/R members will be recruited				
Data Cleaning, Analysis, Manuscript, and Report Tasks				
Task 13: Enter and clean study data (lab values, adverse events, self-report data, IVR data)	X	X	X	
Task 14: Perform analyses germane to Aims 1, 2, and 3				
Task 15: Write and submit necessary reports to DoD	X	X	X	
Task 16: Write and submit manuscripts				
Data Cleaning, Analysis, Manuscript, and Report Milestones: Tasks 13 through 16 will be completed by the end of the grant period.				

Recruitment Figures Update:

Target Enrollment Table				
Period	Dates		Target Enrollment	Actual Enrollment (as of 12/4/16)
Year 1	Q1	12/3/2013 to 3/3/2014	0	0
	Q2	3/4/2014 to 6/3/2014	0	0
	Q3	6/4/2014 to 9/3/2014	0	0
	Q4	9/4/2014 to 12/3/2014	0	0
Year 2	Q1	12/4/2014 to 3/4/2015	0	0
	Q2	3/5/2015 to 6/4/2015	3	3
	Q3	6/5/2015 to 9/4/2015	4	4
	Q4	9/5/2015 to 12/4/2015	2	2
Year 3	Q1	12/5/2015 to 3/4/2016	1	1
	Q2	3/5/2016 to 6/4/2016	3	3
	Q3	6/5/2016 to 9/4/2016	1	1
	Q4	9/5/2016 to 12/4/2016	21	2
Year 4	Q1	12/5/2016 to 3/5/2017	21	
	Q2	3/6/2017 to 6/5/2017	21	
	Q3	6/6/2017 to 9/5/2017	21	
	Q4	9/6/2017 to 12/5/2017	22	
Total		12/3/2013 to 12/6/2018	120	16

What opportunities for training and professional development has the project provided?
Nothing to Report

How were the results disseminated to communities of interest?
Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?
We have been unable to meet our goal of enrolling 20 participants in our second full year of recruitment. In the next reporting period we plan to continue to hone recruitment strategies by strategically recruiting likely eligible vets through our addiction treatment clinic, through community veteran organizations, continuing with our contact of veterans identified as likely candidates through the results of our data access request and through VA wide listserv emails.

We have also requested IRB approval (submitted November 10, 2016) to recruit potential study participants through a decision support tool located in the VA Computerized Patient Record System (CPRS), called “Clinical Reminders”. The clinical reminder is an interactive dialog which allows staff to click boxes linked with text that is pertinent to the care they are giving. If this amendment is approved it should make it much easier for providers to inform their patients about the study and thereby increase referrals. We have also begun working with the Clinical Studies Unit at the American Lake division of VA Puget Sound to arrange for staff there to support the study by flyering and providing space and staff assistance with visits. No additional IRB approvals are needed for us to set up a site at American Lake but as of 12/4/16 the

psychiatrist who has agreed to assist with study safety visits had not yet finished the necessary tasks for IRB approval to see study participants. Finally, we consulted with Col. James McKnight from the CDMRP and he has agreed to see if he can help facilitate recruitment of National Guard members at Camp Murray.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

   What was the impact on the development of the principal discipline(s) of the project?
   Nothing to Report

   What was the impact on other disciplines?
   Nothing to Report

   What was the impact on technology transfer?
   Nothing to Report

   What was the impact on society beyond science and technology?
   Nothing to Report

5. **CHANGES/PROBLEMS:**
   Meeting recruitment goals remains an issue for the project. We continue to explore new and additional recruitment/retention strategies, as described in our previous quarterly reports and the rest of this report.

   Changes in approach and reasons for change
   Nothing to Report

   Actual or anticipated problems or delays and actions or plans to resolve them
   During this reporting period both our study coordinator and our study clinician left for other positions. While they both provided ample notice and did their best to make the transitions smooth, orienting and training the new study staff initially took time that could not be devoted directly to pursuing new recruitment avenues. Fortunately both our new study coordinator and our new study clinician are incredibly experienced and competent so we have been able to make nice headway in establishing both an additional site (American Lake) and a potentially very strong new way of recruiting (through the medical record clinical reminder system). Additionally, although the psychiatrist at American Lake was hired there in August, he was unable to complete the IRB trainings needed until November, introducing significant delays in getting set up there. As noted above, this has now been accomplished and together with the support of the Clinical Studies Unit down there and the increased mobility of our Seattle-based study clinician, we are poised to be able to increase recruitment markedly in 2017.

   Changes that had a significant impact on expenditures
   None. The staffing changes noted above were kept as revenue neutral as possible with only minor increases in overall staffing costs, and the fees to be paid to the American Lake Clinical Studies Unit staff are nominal.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to Report

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Nothing to Report

- **Website(s) or other Internet site(s)**
  Nothing to Report

- **Technologies or techniques**
  Nothing to Report

- **Inventions, patent applications, and/or licenses**
  Nothing to Report

- **Other Products**
  Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

Name:	*Tracy Simpson, PhD*
Project Role:	*Co-PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1.8*
Contribution to Project:	*Dr. Simpson is the study PI.*
Funding Support:	*Dr. Simpson's salary is supported by VAPSHCS*

Name:	*Andrew Saxon, MD*
Project Role:	*Co-PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1.2*
Contribution to Project:	*Dr. Saxon is co-study PI*
Funding Support:	*Dr. Saxon's salary is supported by VAPSHCS*

Name:	*Robert Lyons*
Project Role:	*Research Coordinator*

Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*7*
Contribution to Project:	*Participant recruitment and regulatory duties*
Funding Support:	*N/A*

Name:	*Dana Tell, ARNP*
Project Role:	*Study Clinician*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*9.6*
Contribution to Project:	*Performs in-person participant visits*
Funding Support:	*N/A*

Name:	*Kimberley A. Hodge*
Project Role:	*Research Coordinator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*3.1*
Contribution to Project:	*Participant recruitment and regulatory duties*
Funding Support:	*Ms. Hodge's salary also supported by NIH (R01AA020252) and DoD (W81XWH-15-1-0330) funds, for separate effort on those projects.*

Name:	*Carol Achtmeyer, MN, ARNP*
Project Role:	*Study Clinician*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*0.6*
Contribution to Project:	*Performs in-person participant visits*
Funding Support:	*The remainder of Ms. Achtemeyer's salary is supported by VAPSHCS for effort on other projects.*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to Report

What other organizations were involved as partners?
Nothing to Report

8. **SPECIAL REPORTING REQUIREMENTS:** See included quad chart

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. **APPENDICES:** See attached Quad Chart.

Effect of Prazosin and Naltrexone on Script Induced Alcohol Craving in Veterans with Alcohol Use Disorders with and without Co-occurring PTSD

11152009 / W81XWH-14-1-0025

PI: Tracy Simpson, PhD / Andrew Saxon, MD **Org:** Seattle Institute for Biomedical and Clinical Research **Award Amount:** $802,000

Approach

Recently deployed Veterans are at risk of developing hazardous drinking patterns post-deployment. Craving is strongly associated with continued problematic use and relapse. The noradrenergic system subserves craving-related brain systems. Blocking α1 receptors with the noradrenergic antagonist, prazosin, has the potential to modulate craving.

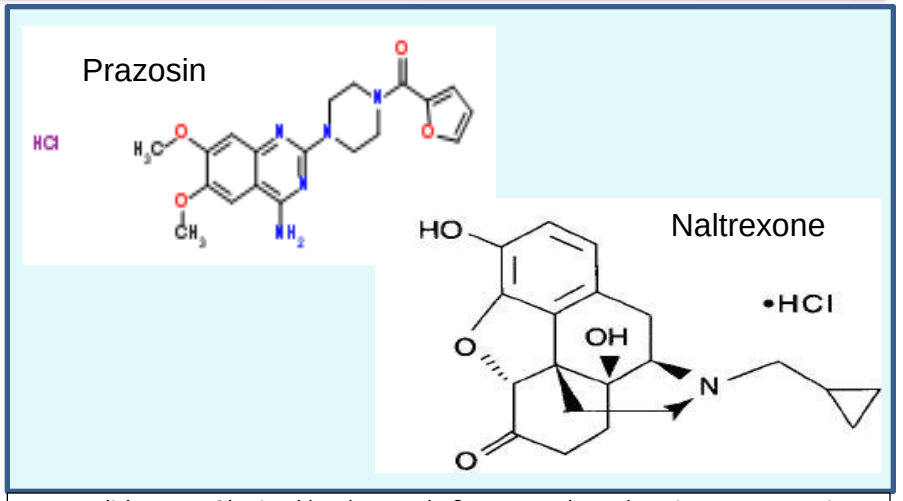
120 Veterans with an alcohol use disorder (AUD) will be randomized to receive prazosin, naltrexone, both medications, or placebo for 3 weeks. Craving will be assessed through daily monitoring and a laboratory based craving induction paradigm.

Study Aims

Specific Aim 1: To compare the effects of prazosin only, naltrexone only, and their combination to placebo control on reward oriented and relief oriented alcohol craving elicited in a human laboratory setting.

Specific Aim 2: To determine the effect of the four medication conditions on day-to-day reports of alcohol craving and drinking motives.

Specific Aim 3: To explore whether PTSD status moderates medication response.



Accomplishments: Obtained local IRB and R&D approvals; undergoing DoD IRB review; research staff hired; daily monitoring system constructed; pharmacy & lab interfaces established; compounding pharmacy interface established.

Timeline and Cost

Activities	CY 13	14	15	16	17
Preparatory Tasks					
Recruitment/Retention					
Enter and clean study data					
Analyze data for Aims 1, 2 & 3; write and submit manuscripts					
Estimated Budget ($K)		**$139k**	**$207k**	**$212k**	**$244**

Budget Expenditure to Date: Projected Expenditure: $212,150
Annual Expenditure (includes $18,600 in outstanding invoices): $195,702

Goals/Milestones ☑☑☑ ☐☐☐

CY14 Goals
- ☑ Obtain all necessary regulatory approvals
- ☑ Prepare staff; compound meds; set up lab and IVR.
- ☑ Initiate recruitment and retention efforts
- ☐ 20 Veterans recruited by the end of year 1

CY15 Goals
- ☐ 60 Veterans recruited by the end of year 2
- ☑ Enter and clean study data

CY16 Goals
- ☐ 100 Veterans recruited by the end of year 3
- ☑ Enter and clean study data

CY17 Goals
- ☐ 120 Veterans recruited by half way through year 4
- ☐ Perform date analyses for Aims 1, 2, and 3.
- ☐ Write and submit manuscripts

Comments/Challenges/Issues/Concerns

- We were unable to reach our projected recruitment goal this year but have submitted an IRB request to add an easier way for providers to inform their patients & provide referrals.
- The need to train a new study coordinator and study clinician delayed study recruitment efforts while they were brought up to speed.

Updated: 12/22/16